

GUEST EDITORIAL

“Extended” Lymph Node Dissections for Gastric Cancer—Is More Better?

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It has been known for some time that the overall results after operations for gastric cancer in Japan are far superior to results that have been obtained in the United States and Europe [1]. A number of non-randomized comparisons have supported the concept that these improved results in Japan might be due to the use of more extensive regional lymph node dissections [2–7]. Since lymphatic spread has long been recognized as a major prognostic determinant for gastric cancer, this is not surprising.

Other factors confuse the issue, however. The possibility of underlying racial or ethnic differences in these populations has been suggested as a possible cause [8]. However, the major factor has been differences in stages between the various populations at the time they undergo operations. Specifically, the proportion of cancers that are “early gastric cancer”, which result in a much better survival rate, has progressively increased in Japan since the 1950s. This has not been the case elsewhere in the world. It has been suggested that the differences in postoperative outcomes are attributable to difference in stage, rather than the extent of lymphadenectomy. Nevertheless, the results are actually better for each stage, in Japan, when they are broken down in terms of American Joint Committee on Cancer (AJCC) staging [9]. Of concern is that more extended dissections could actually “upstage” patients, when compared with the stage classification in patients who are subjected to only “standard” lymph node dissections since additional nodal tissue is examined. In spite of these explanations, Japanese surgeons are convinced that extended lymphadenectomy is the major reason for their success, which is impressive.

Japanese surgeons have developed a uniform classification of gastric resection in terms of the extent of stomach removal and lymph node dissection using a rather complex staging classification for lymph nodes (N1–N4). The Japanese terminology for this classification is somewhat different than the AJCC classification (which does not

consider N3 and N4 nodes as regional nodes) and the classification of the extent of lymph node dissection relates to this anatomic staging classification. The classification for extended resection is also related to the anatomic location of the primary cancer in the stomach (as shown in Figure 1 [10]). The Japanese categories of resection under discussion are:

1. R1 resection, which includes en bloc dissection of N-1 nodes as defined in the TNM classification.
2. R2 resection, which includes N-1 and N-2 nodes. If subtotal gastrectomy is employed for a more distal lesion, the spleen and distal pancreas are *not* removed. With more proximal lesions requiring total gastrectomy, splenectomy is performed and distal pancreatectomy is included if the serosa, greater curvature, or posterior wall of the stomach is involved.
3. R3 resection means complete resection of the N1 and N2 nodes and, in addition, N3 lymph nodes (nodes along the hepatoduodenal ligament and at the root of the mesentery). The latter are generally considered distant metastasis in the AJCC classification.

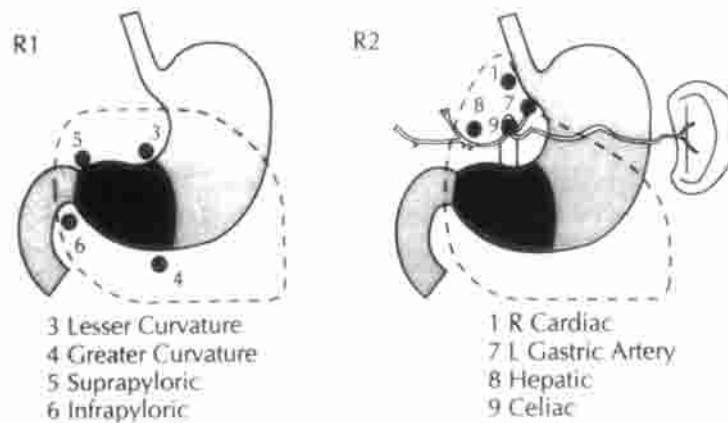
There are multiple reports from the Far East supporting extended lymphadenectomy [2,3,5,6] and, more recently, apparently successful efforts to emulate these results have been reported from the West by Siewert et al. [4], Jatzko et al. [11], and by Volpe et al. [7]. These reports of

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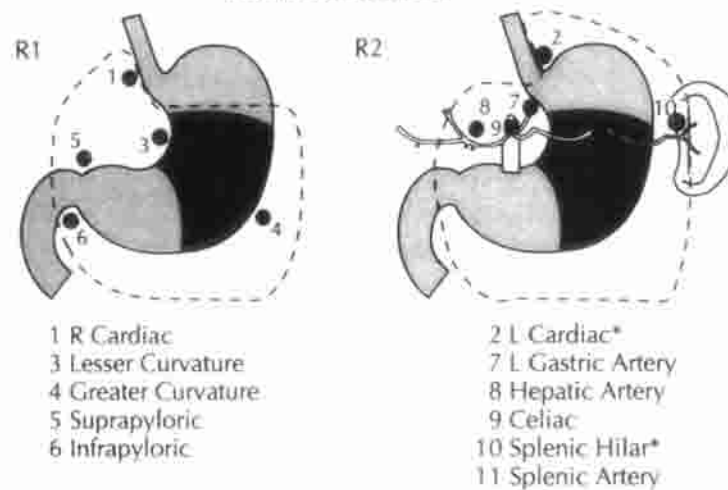
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Lower Third Lesions



Middle Third Lesions



Upper Third Lesions (Includes Cardia)

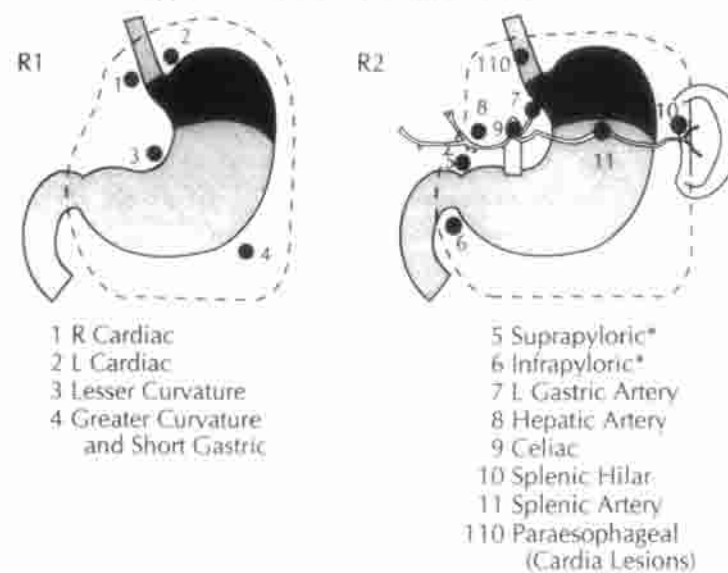


Fig. 1. The scope of gastric lymphadenectomy based on the location of the primary cancer. Reprinted with permission of the American Medical Association, the Publisher, from Smith JW, Shiu MH, Kelsey L, and Brennan MF: Morbidity of radical lymphadenectomy in the curative resection of gastric carcinoma. Arch Surg 126: 1469-1473, 1991. Copyright 1991, American Medical Association.

non-randomized comparisons of the outcomes following extended lymph node dissection with earlier results have further increased the suspicion that extended lymphadenectomy is “better”.

Before addressing recent randomized trials of the various types of lymphatic dissection used for gastric cancer, it is worthwhile to review earlier information that has led to our bias in the United States towards a more conservative lymphadenectomy. After armchair enthusiasm in earlier years for the potential benefit of extensive lymphadenectomy achieved by routine “extended total gastrectomy” [12], one of us (W.L.) compared the overall results of gastric resection for cancer during two successive time intervals at a major cancer center [13]. The first interval (1945–1950) was an era when the resection policy was “conservative” (i.e. R-1 dissection). The second time period was 1950–1955, a period in which more than half of the gastric cancer patients at the same cancer center were treated by an “extended total gastrectomy”. This procedure entailed routine resection of the body and tail of the pancreas, and the spleen, in order to remove the secondary orbit of lymph nodes, the so called pancreaticolienal nodes [12]. (This operation is appropriately designated as an R-2 resection). Assessment of the survival of *all* patients for these two time periods at this cancer center in 1960 failed to show any differences in overall survival, nor was there a difference in survival for patients undergoing “curative resection” during these two time periods.

This lack of survival benefit in the later period, when a curative resection emphasized more extensive lymphadenectomy, led to a significant revision of our earlier thoughts on extended operation. Gilbertson’s analysis of 1,983 cases of gastric cancer at the University of Minnesota operated on between 1936 and 1963 echoed these findings [14]. During an earlier interval (1936–1958), when conservative resection was the order of the day, the operative mortality was lower and the overall survival slightly higher than in the later period (1958–1963) when there was widespread use of extensive lymph node dissections. This finding was similar to our own. Nevertheless, the recently reported data on what appears to be improved results following extended lymphadenectomy again open this question [15].

We often develop enthusiasm for a new treatment approach, based on non-randomized comparisons, only to be disappointed when a subsequent randomized clinical trial fails to support our initial concepts based on “historic controls”. Elective lymph node dissection for malignant melanoma is one example. In this regard, there have been two completed randomized clinical trials of extended lymph node dissection for gastric cancer and both have failed to show benefit from the more extensive (R-2 or D-2) type of lymph node dissection [16,17]. However, the number of patients in each of these trials was quite small. Even those of us who are skeptics regarding the

value of extended lymphadenectomy fail to feel our bias supported by these two small trials. A much larger trial, recently reported from The Netherlands—a prospective randomized comparison of R-1 with R-2 dissection—evaluated adherence in this trial to specific surgical pathologic guidelines. Although the overall design and size of this trial, including significant efforts to standardize the operations, gave hope of obtaining a convincing answer to the question posed, early observations on “noncompliance” (i.e. performance of less dissection than specified) are concerning [18]. The likelihood of detecting a potential therapeutic advantage from a more extensive lymph node dissection appears undermined somewhat by this “noncompliance” of surgeons in terms of the trial assignment for R-1 or R-2 dissection. The increased standardization now required in this trial will delay the definitive answer, but an early concern is that the morbidity with the more extensive dissection is clearly increased in this trial [19].

We must await the long term results of The Netherlands trial before drawing definitive scientific conclusions regarding the benefit, or lack thereof, from extended lymphadenectomy for gastric cancer. On the other hand, we should look at this concept of extended lymphadenectomy in a broader sense in the prolonged interim period before adequate scientific data are available. Let us look at our ideas and experiences with the extended lymphadenectomy concept when it is applied to other solid tumors treated by surgical removal.

Breast carcinoma is a cancer for which similar questions were raised in prior years. Halsted, and later Wangenstein, extended radical mastectomy to include ipsilateral supraclavicular nodes in the resection, only to abandon this approach at a later date because of dissatisfying results. A concerted effort to extend the perimeter of the resected lymph nodes was the addition of internal mammary node dissection to radical mastectomy, an operation effectively developed and described by Jerome Urban [20]. Many of us were convinced at the time of the positive value of this operation for some subsets of breast cancer patients (primarily medial quadrants and central lesions) until later data from several sources demonstrated no survival benefit for this approach. A randomized study comparing extended radical mastectomy with simple mastectomy and radiation showed no benefit from extended operation in this comparison [21]. Caceres from Lima, Peru, using sequential historic periods for comparison, as we did with subtotal gastrectomy and extended total gastrectomy, failed to find survival benefit from the addition of internal mammary node dissection to radical mastectomy [22]. Although these relatively preliminary non-randomized comparisons failed to encourage a formal trial, an international cooperative randomized clinical trial was initiated, and completed, and it confirmed the lack of benefit predicted by these earlier non-randomized

observations [23]. Veronesi and Valagussa extended the observations from this same trial to ten years and showed that disease-free survival and survival were essentially equal in those groups randomized to Halsted radical mastectomy and the same operation plus internal mammary node dissection [24]. Now, the question of value of extension of lymphadenectomy for breast cancer beyond standard axillary node dissection is of historic interest only!

How about results after surgical treatment of another common cancer, carcinoma of the colon or rectum? Lymphatic spread has a major impact on the prognosis of this disease, as we all know, and it was not surprising that the concept of more extensive lymphadenectomy was proposed for this cancer. The left side of the colon was addressed, in this context, since potential lymph node dissections associated with resections of the descending colon, sigmoid colon and rectum can be quite variable in terms of the extent of dissection. For rectal cancer a more extensive lymph node dissection would include ligation of the inferior mesenteric artery at the aorta rather than ligation distal to the left colic branch, and would allow removal of additional lymph nodes as well as requiring a more extensive bowel resection. Grinnell at Columbia, one of the surgical leaders utilizing this approach, carefully studied tumor involvement of the specific group of nodes removed by the higher ligation [25,26]. Follow-up results were disappointing when these additionally resected nodes had tumor involvement. Grinnell concluded that this extension of lymph node dissection had no real value!

An even more aggressive approach to extended lymphadenectomy for cancer of the distal colon and rectum was proposed by Michael Deddish in 1951 [27]. This was an abdominopelvic lymph node dissection (including iliac and para-aortic nodes). His initial report of 25 patients described tumor-involved nodes in this additionally resected lymph node basin in 24% of the patients operated on. This same approach was later encouraged by Block and his colleagues, who concluded that the overall results of operation were enhanced by this extended lymphadenectomy [28]. However, the five-year results of this operation reported from Dr. Deddish's surgical service at the Memorial Hospital (New York City) in 1959 by Stearns and co-workers [29] led to their conclusion that this extension of lymphadenectomy was not beneficial. No significant improvement in survival was obtained while postoperative morbidity was greatly increased. Subsequent to this, Bacon and Khubchandani [30] argued that this extension of lymphadenectomy might be beneficial and they "predicted" a 7% increase in survival as a result of this extended operation. There may not be absolutely uniform agreement regarding the lack of value of extending the lymphadenectomy for colon and rectal cancer, but virtually all surgeons in the U.S. now employ a dissection of lymph nodes for colon and rectal cancer that would be

the counterpart of the R-1 dissection used for gastric cancer, rather than employing extended lymphadenectomy. All agree that a reasonable regional lymph node dissection can be curative when limited regional node spread has occurred but, as with breast cancer, an extended lymphadenectomy seems to add no clear-cut survival benefit.

Let us return to the question of the role of extended lymphadenectomy for gastric cancer. It is apparent at international surgical and oncologic meetings that the Japanese consider this question already answered in the affirmative. The surgeons in the Western world, with a few exceptions, are generally skeptical, for the reasons mentioned, that these potentially morbid operations are worthwhile. As two surgeons who have lived and worked through the years of the swinging pendulum on this issue for both gastric cancer and the other cancers discussed, we think when trials on gastric cancer are complete that the final answer to this question will be—more is *not* better!

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